

EXHIBIT 94

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Methodology and Utility of a Job-Exposure Matrix

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We have previously reported a study in which a job-exposure matrix was applied to census data, identifying, e.g., polychlorinated biphenyls (PCBs) and creosote as increasing the risk of urothelial cancer. In this article, we expand on some theoretical issues, and present detailed accounts of constructed linkages for PCBs, creosote, and phenols. For agents of interest, one should emphasize the positive predictive value rather than the sensitivity in the construction of the matrix. The reverse is true for confounding factors; to avoid residual confounding after restriction to subjects unexposed for the confounding factors, one should emphasize sensitivity, possibly compromising the positive predictive value. This discrepancy between agents of interest and confounding factors may limit the application of a general matrix for studying several different diseases. The construction of the matrix is much harder, if sensitivity rather than positive predictive value is emphasized for an agent. Confounding from industry-related agents arises due to a true mixed exposure in certain work tasks, but also due to a gross classification of occupations in the census. One should not confuse different levels of the positive predictive value with exposure dose. A "dose-response" with different levels of positive predictive value reflects an accuracy of the matrix, not a biological phenomenon. Studies with exposure information from a job-exposure matrix applied to registers with scant information on occupation and industry may be warranted for exposures and diseases for which previous studies with a detailed documentation of exposure have low precision. © 1993 Wiley-Liss, Inc.

Key words: cohort study, confounding, etiology, job-exposure matrix, positive predictive value, occupation/industry classification, occupational exposures

INTRODUCTION

In many countries, information on occupational titles and industrial categories is contained in large administrative registers that cover, e.g., the entire population or all employees in a certain company. These registries are a tempting source for epidemiologic studies, since they can be linked to other registries that give health outcomes, for example, to a national cancer register. Such research might be cost-effective, and involve a large study population, giving a high precision in risk esti-

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mates. Moreover, differential exposure misclassification ("recall bias") between cases and referents, and misrepresentation ("selection bias"), potential problems in a case-referent study, are presumably avoided.

A major limitation in the registers is the lack of detailed information related to agents of interest, for example, certain industry-related chemicals. One example is the Swedish Cancer Environment Register, a computerized linkage between the National Swedish Census of Population 1960 and the Swedish Cancer Register 1961–1979. In this data base, information on "exposure" is limited to an occupational title and industrial category for each subject at one time during 1960. To focus on specific agents, information has to be added to the register, for example, by a job-exposure matrix.

A job-exposure matrix may be defined as a cross-classification between a list of job titles and a list of agents to which persons carrying out the jobs may be exposed [Acheson, 1983]. The elements of the matrix indicate the presence or absence of exposure within each job title, but additional elements may be incorporated, e.g., indicators of the level of exposure, and the percentage of the population exposed. A matrix may be called a general job-exposure matrix, if it covers all job titles in a nationwide classification of occupations, and contains a large number of agents for which several different outcomes can be studied. A specific matrix may be restricted to, for example, a selected subset of job titles. Such a matrix often contains a limited number of agents and is often developed for the study of just one disease. Restricted matrices have, for example, been used in studies of the association between physical activity and colon cancer [Gerhardsson et al., 1986], and combustion gases and urinary bladder cancer [Thériault et al., 1984].

One may choose to link occupational titles, industrial categories, or a combination of these classifications (work tasks) for linkage with exposures to different agents. We developed a matrix for a study of urothelial cancer with linkages between 57 selected agents/groups of agents and all work tasks as reported in the 1969 National Census of Population in Sweden [Plato, 1987; Steineck et al., 1989]. The results indicated that, for example, exposure to PCBs and creosote are associated with urothelial cancer.

Job-exposure matrices have been used mostly in case referent studies [Pannett, 1990]. Some problems are more pronounced, or specific, e.g., adjustment for confounding factors, when a job-exposure matrix is developed for a large-scale cohort study as compared to a case-referent study, as discussed in our previous report [Steineck et al., 1989]. Here we want to discuss further the construction of the matrix, give some additional comments on the potential usefulness of a matrix, and expand on some theoretical issues. For 3 of the 57 agents—PCBs, creosote, and phenols—we present detailed accounts of the constructed linkages (Tables I, II, and III). Publication of the whole matrix is pending [Plato and Steineck, 1992].

CONSTRUCTION OF THE MATRIX

Choice of Agents

The agents and groups of agents chosen for the matrix are known or suspected carcinogenic agents [Steineck et al., 1989]. Because of the widespread belief that the aromatic amines β -naphthylamine, 4-aminodiphenyl, and benzidine are associated with urothelial cancer, 11 additional specific aromatic amines were included.

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TABLE I. Excerpt From the Job-Exposure Matrix: Application to Polychlorinated Biphenyls (PCBs)

Occupational title	Industry category	Substance(s)	Positive predictive value
Train engineers	Railways	PCBs	Low
		Diesel exhausts	Low
Electrical fitters and wiremen	Electrical power stations	Asbestos	High
		PCBs	Moderate
		Naphthalenes	Low
		Heavy metals	Low
		Chlorinated hydrocarbons	Low

Broad categories had to be chosen, since, for most agents, it was unlikely that workers exposed to the specific substances could be distinguished. Such broad categories include chlorinated aliphatic hydrocarbons, pyrolysates, heavy metals, cutting fluids, and cutting oils. Also, broad “non-specified categories” had to be included for aromatic amines when it was impossible to sort out the detailed exposures. We selected three such categories: aromatic azo pigments, non-specified aromatic amines, and non-specified dyes containing aromatic amines.

For each agent, we had to decide whether to emphasize sensitivity or positive predictive value in the classification of exposure (see definition in Fig. 1). It was probably inevitable that a high sensitivity would decrease the positive predictive value, and vice versa. A decreased sensitivity may affect precision and validity. A decreased sensitivity in the classification of exposure has a negligible impact if the unexposed group is many times larger than the exposed group [Partanen, 1987]—as is the case with the present matrix (hypothetical example in Table IV). A few truly exposed subjects with a higher incidence of the disease will only marginally affect the incidence among those categorized as unexposed, and, thus, not affect the ratio between exposed and unexposed (relative risk). Moreover, for most agents, we did not expect precision to be a problem.

Predictive Value

When using a job-exposure matrix as a means of exposure classification, a high positive predictive value rather than sensitivity is crucial for the validity of the study (see definition in Fig. 1). Optimally (positive predictive value of 1.00) all categorized as exposed are truly exposed. For example, if the “true” relative risk of an outcome among the exposed group is 2.0, but the exposed group includes 4/5 unexposed subjects, the estimated relative risk would only be 1.2.

For β -naphthylamine, 4-aminodiphenyl, and benzidine, our interest was not in the agents per se. Instead, we wanted to eliminate those agents as possible confounding factors. We attempted to avoid confounding by restriction. In this situation, it is essential to emphasize sensitivity over specificity—we wanted to be sure that the subjects exposed to agents showing an increased risk were free from confounding exposure to aromatic amines. The hypothetical example in Table V illustrates how decreased sensitivity in the classification of a confounding factor can give a spuriously increased risk.

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TABLE II. Excerpt From the Job-Exposure Matrix: Application to Creosole/Creosote

Occupational title	Industry category	Substance(s)	Positive predictive value
Tanners	Tannery	Creosole	Moderate
		Phenol	Moderate
		Naphthalene	Moderate
		Chlorinated phenols	Moderate
		Antracene	Moderate
		Auramine	Moderate
Electrical repairmen (line workers)	Electrical power companies	Creosote	Low
Telegraph repairmen (line workers)	Telephone and telegraph companies	Creosote	Low

TABLE III. Excerpt From the Job-Exposure Matrix: Application to Phenol

Occupational title	Industry category	Substance(s)	Positive predictive value
Stationary engine and related equipment operators	Heat production plants	Asbestos	Moderate
		Combustion gases from coal	Moderate
		Combustion gases from oil	Moderate
		Benzene	Low
		Phenol	Low
		Coal tar	Low
Building caretakers	Building service	Asbestos	Moderate
		Phenol	Low
		Chlorinated phenols	Low
		Solvents	Low
		Combustion gases from coal and oil	Low
		Soot from coal and oil	Low

Thus, for all agents except β -naphthylamine, 4-aminodiphenyl, and benzidine, we emphasized the positive predictive value over the sensitivity in the construction of the matrix; for the three aromatic amines, we did the reverse.

We anticipated that for some agents, the balance between precision and positive predictive value had to be achieved with the results at hand. Thus, we chose to have three levels for the positive predictive value; 10–33% (low), 34–66% (moderate), and 67–100% (high). Thus, we could include in the analysis subjects with a low or moderate positive predictive value when an estimate based on subjects with a high positive value was imprecise due to small numbers. Initially, we found it hard to think in terms of “work tasks,” a combination of occupational title and industrial category. The census of population from 1960 (FoB 60) that classifies subjects in three-digit categories was used for occupation. It follows the International Labor Organization (ILO) Classification. The Swedish Standard Industrial Classification of all Economic Activities from 1960 (NGR 60), which follows the International Standard Industrial Classification (ISIC) Classification, was used for three-digit categories for industry. The census included 292 occupation and 308 industry categories defining a large

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		True	
		Exposed	Nonexposed
Classified	Exposed	True positive (TP)	False positive (FP)
	Nonexposed	False negative (FN)	True negative (TN)

$$\text{Sensitivity} = \frac{\text{Number of subjects truly exposed and classified as exposed}}{\text{Total number of subjects truly exposed}} = \frac{TP}{TP+FN}$$

$$\text{Specificity} = \frac{\text{Number of subjects truly nonexposed and classified as nonexposed}}{\text{Total number of subjects truly nonexposed}} = \frac{TN}{FP+TN}$$

$$\text{Positive predictive value} = \frac{\text{Number of subjects truly exposed and classified as exposed}}{\text{Total number of subjects classified as exposed}} = \frac{TP}{TP+FP}$$

Fig. 1. Definitions of positive predictive value, sensitivity, and specificity in construction of job-exposure matrix.

TABLE IV. Hypothetical Example of Decreased Sensitivity of Exposure*

	Exposed	Unexposed
True number of events of disease	100	5,000
True number of subjects	10,000	1,000,000
Rate ratio	2.0	
Sensitivity in exposure 0.5		
Shown number of events of disease	50	5,050
Shown number of subjects	5,000	1,005,000
Rate ratio	1.99	

*Relative risk changes from 2.00 to 1.99, when the sensitivity in the classification of exposure was 50% in this population with a large number of unexposed subjects, as compared to exposed.

number (292 × 308) of work tasks for the matrix. Thus, in the first step, the construction of the unexposed group for the matrix, we eliminated from the exposed all occupations in which less than 10% of the subjects were presumed to have been exposed in 1960. Subjects classified as unexposed to all 57 agents/groups of substances comprise a constant unexposed reference group enrolled in all analyses.

We did, however, deviate somewhat from this scheme, when it was obvious that a certain work task contained a substantial proportion of exposed subjects, although the occupation category of the work tasks has less than 10% exposed subjects. For example, less than 10% of process workers are probably exposed to phenol, but a substantial proportion of the process workers in plastic industries are probably exposed to this agent.

Definition of Exposure

The whole construction of the matrix is a matter of estimated appraisal, since exposure level measurements from 1960 are almost entirely lacking. We deliberately

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TABLE V. Hypothetical Example of Decreased Sensitivity of Confounding Factor*

	Exposed to agent, not to confounder	Unexposed to both	Exposed to both agent and confounder	Unexposed to both
True number of events of disease	50	5,000	100	5,000
True number of subjects	10,000	1,000,000	10,000	1,000,000
Rate ratio		1.0		2.0
Sensitivity of confounder 0.5 ^a				
Shown number of events of disease	100	5,000	50	5,000
Shown number of subjects	15,000	1,000,000	5,000	1,000,000
Rate ratio		1.3		2.0

*A population with truly 10,000 subjects exposed to an agent of interest but not to a confounder, and 10,000 subjects exposed to an agent of interest together with a confounder. True relative risk for agent of interest is 1.0 and confounder is 2.0. Without misclassification of the confounder, a restriction in the analysis to those not exposed to the confounder gives a relative risk of 1.0. With a 50% sensitivity for the confounder, the relative risk instead is 1.3. Unexposed = unexposed to both agent and confounder.

^a5,000 truly confounder exposed subjects with 50 events of disease depicted as without exposure to confounder but, as true, exposed to agent.

chose imprecise words in the report [Steineck et al., 1989]: "Classification of a subject as exposed required an estimated air concentration in the work environment significantly higher than for the general public or a considerable skin contact with liquids of low volatility." A similar definition is used by Alho et al. [1988]. We also added "at least one hour per week and continuous exposure." In short, subjects were categorized as "exposed," when we thought a possible exposure might have a biological impact. The exposure criteria for each substance are presented in the same publication as the whole matrix [Plato and Steineck, 1992].

Level of Exposure

Assessment of exposure is based on information obtained from textbooks and published papers in industrial hygiene and occupational medicine; direct inquiry of colleagues in industry and trade federations; long personal experience from industry; internal or unpublished reports from industry; personal communications. As conceived, the positive predictive value refers only to the dichotomous quality of exposure assessment (exposed vs. unexposed) and had nothing to do with the intensity of exposure (dosage, level). We could not assess the intensity of exposure for most agents/groups of agents, except for solvents and asbestos. For these two exposures (solvents and asbestos), the positive predictive value could be expected to be close to 1.0 for several work tasks, so we found it reasonable to make an assessment of high and low intensity of exposure. Low exposure means, approximately, exposure to less than half of the hygienic standard (Threshold Limit Value), and high exposure means to more than that level. Thus, any possible effect of the intensity of exposure should not be masked by the varying positive predictive values between work tasks.

Unexposed occupation categories were selected as the first step. In the second step, work tasks were linked to the respective agents, and in the third step, each link was assigned a positive predictive value. Note that the matrix only refers to exposure during 1960.

Application to Polychlorinated Biphenyls (PCBs)

An important use of PCBs is as a constituent of insulation and cooling oils used in the electrical industry [Environmental Health Criteria 2, 1976]. A great potential for occupational exposure has thus been in the manufacture and repair of electrical transformers and capacitors [Maroni et al., 1981]. Rooms with high-power signal boxes can be contaminated with oils containing PCBs both in the air and on the facilities. Thus the workers can be exposed both through dermal contact and inhalation [Nisbet and Sarotim, 1972]. PCBs are also used in electrical cables [Gustavsson et al., 1986] and as an additive in protective paints for ships [Jensen et al., 1972]. Recently, PCBs have also been used as plasticizers in plastics and in carbonless carbon papers [IARC, 1978]. Other sources of PCBs are some hydraulic oils, cutting oils, foundry sand, and printing ink [IARC, 1978].

The background level of PCBs found in the larger cities of Sweden probably originates from central disposal plants [Ekstedt and Odent, 1974]. The general public may also be exposed to PCBs [US Environmental Protection Agency, 1982].

For each substance, the matrix was constructed in a three-step procedure [Steinbeck et al., 1989].

1. A substantial proportion of installation and operation electricians are probably exposed to PCBs in capacitors and transformers. Drivers of electrical trains spend their working day in a room with a high-power signal box, and are exposed to PCBs in the air. In addition, some train drivers refill the transformers with PCB-containing oil.

We could not identify any occupation category (or work task) in which at least 10% of the subjects were exposed to PCBs from electrical cables or bottom dyes for ships, nor from hydraulic oils, cutting oils, glues, foundry sand, or printing ink. Subjects truly exposed from these sources were thus included in the group classified as unexposed to PCBs. Exposure from plastics and carbonless papers did not occur in 1960.

2. The industry category "electric power stations" was combined with installation electricians and operation electricians to form the work task linked to PCBs. Train drivers were combined with the industry category "railway."

3. It is reasonable to believe that at least one-third of the installation electricians and operation electricians in electric power stations were exposed to PCBs. This work task probably, however, includes subjects who were not exposed to PCBs. Thus, we estimated the positive predictive value to be less than 2/3 (moderate) in 1960.

Train drivers include subjects who only work with diesel-driven trains. The proportion of drivers in the respective types of trains is hard to judge, but we assessed the positive predictive value to be low. The level of exposure (not assessed in the matrix) is probably intermittently higher among the electricians, while train drivers have a constant but probably comparatively low exposure level.

Phenol and Phenol-Related Substances

This group includes agents used in many different areas. Phenol has mainly served as a disinfectant in the health care industry. It is also a raw material in the

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manufacture of phenol plastics, certain drugs, and paints. Coal tar includes varying amounts of phenol, and tar from coke-producing plants contains about 0.5% phenol.

Commercially available creosote is a mixture of the distillation fractions of carbol oil, naphthaline oil, and anthracene oils. More than 160 different substances have been identified in creosote, mostly with two to six benzene rings. In Finland, creosote has been reported to contain aromatic amines, for example aminoflouren in 0.1–0.3% [Nestler, 1974]. In Sweden, most of the creosote was used in the impregnation of wood. Workers are exposed to creosote by aerosol components, by inhalation, and by dermal contact. Work tasks with exposure include distillation of coal tar, wood impregnation with creosote, and the handling of impregnated wood. A significant formation of aerosol components of creosote occurs when creosote is heated, for example, when a railway is repaired and creosote-impregnated sleepers are close to welding sparks, or when a pole is heated by the sun. Creosote contains creosole, which is found in tanneries [Tideström, 1957; Kolsch, 1953].

The three-step matrix for creosote is as follows:

1. Probably, at least 10% of the line workers were exposed to creosote when climbing poles on sunny days. Also, tanners were exposed. Wood impregnators were classified under the category "wood work, others," and they probably did not constitute 10% of this group so they are classified as unexposed. Also, employees in the railway who work with cross ties probably constitute less than 10% for any appropriate occupational title. Again, the matrix is too rough to be able to include these workers as exposed.

2. Line workers, who climb on poles, work in the industry categories "electric power stations" and "telephone and telegraph companies." The tanners work in the industry category "tanning."

3. It is uncertain what proportion of line workers perform the work mentioned; the positive predictive value was assessed as low. The tanners may encounter different chemical activities, and the positive predictive value was assessed as moderate.

The matrix for phenol is as follows:

1. Workers are mainly exposed to phenol as impurities in carbon tar. Process workers and laborers who deal with phenol-containing materials, used during manufacture of drugs, perfumes, washing detergents, paints, and explosives, probably did not constitute 10% of their respective occupation categories, and were classified as unexposed. Machinists were exposed to phenol in tar. Tanners were exposed to phenol as a disinfectant in different work activities [IARC, 1981]. Caretakers of buildings and cleaners were exposed to phenol in detergents.

2. Machinists (stationary engine and related equipment operators) were exposed to phenol work in coal-fired electric power stations and gas works. Tanners were linked with tanning, cleaners with all different industry categories, and building caretakers with maintenance and real estate caretaking.

3. We estimated that between one-third and two-thirds of the land machinists in

electric power stations and gas works are exposed to phenol (moderate positive predictive value).

GENERAL RESULTS AND DISCUSSION

Terminology varies between authors. We use "occupational title" and "industrial category" to define a work task. Similarly, Pannett et al. [1985] linked "occupational units" and "industrial units" to define job groups. Their occupation units and industry units are collapsed groups of occupational titles and industrial categories.

The number of work tasks with exposed subjects varies between the agents/groups of substances. For 2,4-diaminotoluene, only one work task (hair dressers in the industry category "hair dressing") was identified, while a low intensity of exposure to solvents was found in 71 work tasks.

Confounding from occupational and non-occupational factors probably gives the major errors that can explain a spuriously increased risk. Data on non-occupational confounding in register-based studies are often scarce, and proxies have to be used [Steineck et al., 1989].

Confounding from occupational factors is probably the crucial problem when considering the usefulness of these types of studies. Occupational confounding originates because of real mixtures of exposure in the study base, but also because the categorization of work tasks, done for administrative purposes, is too rough and cannot distinguish between truly separate occupations. The categorization is, in many instances, much finer for white collar workers than for blue collar workers.

As mentioned above, we employed broad categories a priori when we suspected that occupational confounding would make distinctions between agents impossible. After the construction of the matrix, it became obvious that some distinctions between the chosen categories could not provide additional information. For example, all subjects categorized as exposed to crocidolite (blue asbestos) were also exposed to white asbestos. This probably reflects the true exposure distribution in the study base. Subjects exposed to pesticides based on organic phosphorous acids could not be distinguished from those exposed to chlorinated pesticides.

It was possible to distinguish three solvents; styrene, benzene, and gasoline. Other solvents were grouped together in "non-specified solvents." Cutting oils based on natural oils could (for some work tasks) be separated from water-based cutting fluids, which include several additives that may generate nitrosamines. Diesel and gasoline exhausts have, in certain instances, been separated, but occur together for many work tasks.

The categorization under work tasks would be less rough, if occupations were categorized on a five-digit instead of a three-digit level, that is, with more work task combinations, one could increase the sensitivity in the classification of exposure. For example, specific aromatic amines are included in dye pigments that are used by very specialized workers. These workers cannot be distinguished in this matrix with any reasonable predictive value, while they probably could be studied with a matrix based on occupations defined on a five-digit level.

For PCBs, the matrix would have been quite different, if sensitivity rather than positive predictive value had been emphasized, thus including links with great uncertainty considering the possible exposure. Many truly exposed workers were not

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classified as exposed in the matrix, because we suspected that the positive predictive value was too low. After the follow-up of the matrix in the cancer register, we suggest that PCBs are associated with urothelial cancer [Steineck et al., 1989], an impression not altered by our subsequent case-referent study [Steineck et al., 1990]. Thus, if one starts to believe that the association between PCBs and urothelial cancer is causal, the matrix concerning PCBs is obsolete. In studying other agents, one has to exclude PCBs as a confounder of associations with urothelial cancer, and the emphasis should then be on the sensitivity in the classification of exposure to PCBs, and links with a great uncertainty should be included.

Gérin et al. [1985] used reliability in a three-point scale to indicate the coders' estimates of the degree of certainty that a worker has been occupationally exposed to a selected substance. The coder indicates whether he/she is certain that the exposure took place, thinks it is probable, or considers it possible but not probable. This estimation was achievable in a case-referent study in which each subject was interviewed. In the same material, Siemiatycki et al. [1987] defined the exposure for each substance by concentration \times frequency \times the confidence that the exposure occurred. As recently pointed out by Stewart and Dosemici (personal communication), adding a variable for confidence of assessment for each link in a matrix (including positive predictive value and level of intensity) may facilitate the use of the matrix for several diseases. If an agent is of interest for one disease, the analysis may be restricted to links with a high confidence in the assessment. For another disease, when an agent is a possible confounder, links with a low confidence should also be included in the analysis. In our study, assessment of confidence was built into the construction of the matrix. When we emphasized sensitivity, links were made even if the information was sparse. A "dose-response" with a higher risk for a higher positive predictive value or a higher confidence of assessment does not reflect a biological phenomenon, but it may, for example, reflect accuracy in the appraisal of the positive predictive value.

Categories for the positive predictive value vary between authors [Hoar et al., 1980; Gérin et al., 1985; Ferrario et al., 1988; Kauppinen and Partanen, 1988; Magnani et al., 1988; Dewar et al., 1991]. It is unfortunate that the parameter name "intensity" [Coggon et al., 1984] probably refers to the positive predictive value and, we stress, does not reflect any biological phenomenon or exposure level.

As can be seen from the examples above, it is much more time consuming to put the emphasis on sensitivity rather than on positive predictive value, because one should then not miss any exposed subject in the study base. Thus, for a disease related to several established carcinogens, such as lung cancer, one has to emphasize sensitivity for these potential confounders in the construction of the matrix, making the work very bothersome and, possibly, not worthwhile.

Moreover, when data with a fair precision already exist on an association, a large register study with a job-exposure matrix probably cannot contribute much new information. Few, if any, details on an association can usually be obtained from the registers. Thus, if these kinds of studies have a *raison d'être*, it is for exposures for which the previously published cohorts are small in number and for diseases that, because of low incidence, present with few cases in cohorts in which the exposure is well documented. The main task for register-job-exposure matrix studies is probably to economize on future analytic epidemiological research for such exposures and diseases, by hinting at possible causal hypotheses.

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